Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-3, 5, 6, 10-13 and 35-49 are pending in the application, with claims 1 and 39 being the independent claims. Claim 4 is sought to be cancelled without prejudice to or disclaimer of the subject matter therein. New claims 39-49 are sought to be added. These changes are believed to introduce no new matter, and their entry is respectfully requested.

It is believed that the amendments presented above will place the application in condition for allowance and/or in better form for appeal. *See* 37 CFR § 1.116(a). Specifically, claim 1 has been amended to include a DNA molecule which is at least 90%, rather than 40%, homologous to a DNA molecule of SEQ ID NO:1, and the phrase "or a fragment thereof" has been deleted from claims 1 and 36-38. New independent claim 39, and the newly added claims that depend therefrom, encompass or include subject matter that was originally encompassed by claims 1-6, 10-13, 35 and 36. The amended and new claims therefore do not raise any new issues that would require further consideration and/or search. Thus, Applicants believe that, in accordance with 37 CFR § 1.116(a), the amended and new claims presented above should be entered after final.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Claim Objections

The Examiner has maintained the objection to claim 4 as being dependent upon a rejected base claim, *i.e.*, claim 1. *See* Paper No. 21, page 2. The Examiner, in a prior Office Action, has stated that claim 4 would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. *See* Paper No. 17, page 3.

Although Applicants respectfully disagree with the grounds upon which claim 1 was rejected, Applicants nevertheless have cancelled claim 4 and have added new independent claim 39. New claim 39 encompasses subject matter that was originally encompassed by claim 4. Accordingly, based on the Examiner's indication that claim 4 would be allowable if rewritten in independent form, Applicants submit that new claim 39 (as well as new claims 40-49 which depend directly or indirectly therefrom) should be allowed.

The Examiner has also objected to claims 11 and 35-38 as being dependent upon a rejected base claim, *i.e.*, claim 1. *See* Paper No. 21, page 2. The Examiner stated that these claims would be allowable if rewritten in independent form including all of the limitations of the base claims and any intervening claims. *See id.*

Although Applicants respectfully disagree with the grounds upon which claim 1 was rejected, Applicants have nonetheless amended claim 1 to accommodate the Examiner's rejections and to expedite prosecution. *See* amendments set forth above and the remarks presented below. Accordingly, in view of the amendment to claim 1, Applicants submit that the objection to claims 11 and 35-38 is moot and should be withdrawn.

II. Information Disclosure Statement

The Examiner has acknowledged Applicants' assertion that they did not file an Information Disclosure Statement on February 14, 2000. *See* Paper No. 21, page 3. The Examiner further indicated that reference to "IDS paper no. 9" will be removed from the application cover. *See id.*

The Examiner also requested that "the IDS filed on 12/3/99 be filed with the response to this office action because the IDS filed on 12/4/00[1] is missing." *See* Paper No. 21, page 3, lines 6-8. In order to assist the Examiner and to expedite the prosecution of the application, Applicants submit herewith a copy of the IDS that was filed on December 3, 1999 along with the PTO Form-1449 that was included with the IDS and copies of the documents cited therein. Applicants respectfully request that the Examiner indicate in the official file wrapper of this patent application that the documents have been received and considered.

III. Claim Rejections Under 35 USC § 112, First Paragraph

A. Written Description

The Examiner has again rejected claim 1 under 35 USC § 112, first paragraph. *See* Paper No. 21, page 3. According to the Examiner, "the specification does not provide sufficient description of a genus of polynucleotide sequences that possess any of the

---

[1]Applicants note that no IDS was filed on December 4, 2000. It appears, therefore, that the Examiner intended to indicate that the IDS filed on 12/3/99 "is missing."

biological characteristics of SEQ ID NO:1." *See* Paper No. 21, page 4. The Examiner further stated:

> The as-filed specification does not provide an adequate written description of a representative number of species of DNA molecules with at least 40% homology coding for a AD7c-NTP polypeptide, which functions has an activity of AD7c-NTP when expressed in neuronal cells. . . A mere statement asserting that any sequence having at least 40% homology to the only disclosed AD7C-NTP encoded in SEQ ID NO:1 without providing the essential and specific arrangement of the amino acid residues positioned in the sequence does not lend evidentiary support for a skilled artisan to have recognized that applicant was in possession of the genus of AD7c-NTP encoded nucleic acid sequences as claimed, particularly since the essential element of the coding sequence of a generic AD7c-NTP is lacking from the as-filed specification and since the skill and knowledge in the art is not adequate or conventional to determine the primary sequence of the representative number of species of AD7c-NTP encoded genes or nucleic acids on the basis of the only disclosure of one AD7c-NTP protein encoded in SEQ ID NO:1.

Paper No. 21, page 6.

Applicants respectfully traverse the rejection. Nevertheless, Applicants have amended claim 1. Claim 1, as currently presented, is directed to a DNA construct, which comprises a DNA molecule of SEQ ID NO:1 or a DNA molecule which is at least 90% homologous thereto, wherein said DNA molecule is under control of a heterologous neuro-specific promoter, and wherein said DNA molecule codes for a protein that has an activity of AD7c-NTP when expressed in neuronal cells. Applicants submit that the specification describes the presently claimed invention in sufficient detail such that one skilled in the art would reasonably conclude that Applicants had possession of the claimed invention as of

the effective filing date. *See Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1560, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991).

The Examiner has noted that "the description of the primary sequence of amino acid residues in which the positions of the amino acid residues are particularly arranged is essential for the biological function of the protein encoded by the sequence." *See* Paper No. 21, page 6, lines 6-8. Although the primary sequence of a protein is important for its biological function, the written description requirement may nonetheless be satisfied for a claim to a genus of DNA molecules that are at least 90% homologous to a disclosed nucleotide sequence. This proposition is specifically supported by the USPTO's Synopsis of Application of Written Description Guidelines (hereinafter "Written Description Synopsis").

Example 14 of the Written Description Synopsis involves an analysis of the following claim: "A protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A→B." The specification supporting this claim provides the following information:

> The specification exemplifies a protein isolated from liver that catalyzes the reaction of A→B. The isolated protein was sequenced and was determined to have the sequence as set forth in SEQ ID NO:3. The specification also contemplates but does not exemplify variants of the protein wherein the variant can have any or all of the following: substitutions, deletions, insertions and additions. The specification indicates that procedures for making proteins with substitutions, deletions, insertions and additions is routine in the art and provides an assay for detecting the catalytic activity of the protein.

Written Description Synopsis, Example 14.

The Written Description Synopsis, Example 14, concludes that the disclosure meets the requirements of 35 USC § 112, first paragraph, in part because "procedures for making variants of SEQ ID NO:3 which have 95% identity to SEQ ID NO:3 and retain its activity are conventional in the art." *See id.* Moreover, it is noted that:

> [t]he single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified activity. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus.

Written Description Synopsis, Example 14.

The situation presented in Example 14 of the Written Description Synopsis closely parallels the circumstances surrounding Applicants' claims and the written description provided therefor. As such, Applicants submit that the guidance and instructions provided by the USPTO for analyzing a claim for compliance with the written description requirement mandates that the written description requirement of § 112, first paragraph, is satisfied for Applicants' claims.

First, in Example 14, it is stated that "all variants [encompassed by the claim] must possess the specified catalytic activity and must have at least 95% identity to the SEQ ID NO:3." Similarly, all of the species of DNA construct encompassed by Applicants' claim 1 must have at least 90% homology to SEQ ID NO:1 and must code for a protein having an activity of AD7c-NTP when expressed in neuronal cells.

Second, it is noted in Example 14 that "[t]here is a single species disclosed, that species being SEQ ID NO:3;" and that "[t]here is actual reduction to practice of the single

disclosed species." Likewise, Applicants have disclosed SEQ ID NO:1 in the specification and have shown actual reduction to practice of SEQ ID NO:1. *See* specification at page 33, line 9, through page 35, line 28 (describing the isolation of the AD7c-NTP cDNA and the characteristics of the molecule); *see also* Fig. 1.

Third, according to Example 14, "procedures for making variants of SEQ ID NO:3 which have 95% identity to SEQ ID NO:3 and retain its activity are conventional in the art." Likewise, procedures for making DNA molecules which are at least 90% homologous to SEQ ID NO:1 and which encode proteins that retain the activity of AD7c-NTP are conventional in the art. As stated in the specification, DNA molecules which are at least 90% homologous to SEQ ID NO:1 may be isolated from cDNA libraries of humans and animals by hybridization under stringent conditions to the DNA molecule of SEQ ID NO:1 according to methods known to those of skill in the art. *See* specification at page 19, lines 3-15. Applicants note that many other methods for obtaining DNA molecules that fall within the scope of claim 1 were well known to persons having ordinary skill in the art at the time of the invention; examples include random and directed mutagenesis of a DNA molecule to produce a variant of SEQ ID NO:1 that is at least 90% homologous thereto. In addition, proteins encoded by variants of SEQ ID NO:1 can easily be tested for AD7c-NTP activity using the procedures described in the specification (*see* discussion immediately below) as well as with other methods that are conventional in the art for testing the biological activity of a protein.

Fourth, in Example 14 of the Written Description Guidelines, it is stated that "an assay is described [in the specification] which will identify other proteins having the claimed catalytic activity." Correspondingly, in Applicants' specification, assays are described which

will identify other DNA molecules encoding proteins having an activity of AD7c-NTP. For example, the specification describes the production of transgenic animals which over-express AD7c-NTP and the analysis of such animals for "evidence of neuronal or neuritic abnormalities associated with Alzheimer's disease, neuroectodermal tumors, malignant astrocytomas and gliblastomas." *See* specification at page 20, lines 1-29. The specification also describes an *in vitro* assay for AD7c-NTP activity involving the over-expression of AD7c-NTP in neuronal cells and the analysis of such cells for growth properties and morphology, including the occurrence of apoptosis and neuritic sprouting. *See* specification at page 45, line 16, through page 46, line 26.

As demonstrated above, the hypothetical situation described in Example 14 of the USPTO's Written Description Synopsis is very similar to the situation presented for Applicants' claim 1. Since it is concluded that adequate written description is provided for the hypothetical claim in Example 14, it follows that there is adequate written description for Applicants' claim 1.

Applicants' contention that the written description requirement is satisfied for claim 1 is supported, not only by the USPTO's Written Description Synopsis, but also by the Federal Circuit's interpretation and application of 35 USC § 112, first paragraph. *See, e.g.*, *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). According to the Federal Circuit, the disclosure of a patent must allow one skilled in the art to visualize or recognize the identity of the subject matter of the claim. *See id.* at 1568, 43 USPQ2d at 1406. Applicants have provided in the specification a detailed analysis of the sequence characteristics of the AD7c-NTP cDNA and of the corresponding translated amino acid sequence. *See* specification at page 34, line 6, through page 35, line

28. Applicants have also described various activities possessed by proteins encoded by AD7c-NTP and methods for assaying such activities. *See, e.g.*, specification at page 46, lines 4-26. Moreover, methods for making DNA molecules that are 90% homologous to a reference DNA molecule are common in the field of molecular biology and are also described in the specification. *See, e.g.*, specification at page 19, lines 3-15. In view of these factors, a skilled artisan would be able to clearly visualize and recognize the DNA molecules encompassed by claim 1.

Therefore, based on Federal Circuit precedent and the guidance provided by the USPTO, Applicants submit that there is adequate written description for claim 1. Accordingly, Applicants respectfully request that the rejection of claim 1 under 35 USC § 112, first paragraph, for insufficient written description, be reconsidered and withdrawn.

B. Enablement

The Examiner has also maintained the rejection of claims 1-3, 5, 6, 10, 12 and 13 under 35 USC § 112, first paragraph, as allegedly not being enabled by the specification. *See* Paper No.21, pages 8-9. Applicants respectfully traverse this rejection.

According to the Examiner:

> In view of the state of the art and the as-filed specification, it is apparent that one skilled in the art would be able to determine a DNA sequence with 40 percent identity to SEQ ID No: 1. However, it is not apparent to one skilled in the art if the nucleic acid sequence with at least 40 percent homology to SEQ ID No: 1, would exhibit the same biological function of SEQ ID No: 1. Since, the relationship between a sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g. see Chiu et al., *Folding and Design*, 1998, pp. 223-228), it would require undue experimentation for one skilled in the

> art to arrive at other polynucleotides sequences that have SEQ ID No:1 activity.

Paper No. 21, page 10.

Applicants first note that the rejection for lack of enablement appears to focus a great deal on the inclusion within the claims of DNA molecules that are at least 40% homologous to SEQ ID NO:1. Applicants respectfully disagree with the Examiner's assertion that DNA molecules that are 40% homologous to SEQ ID NO:1 and that encode proteins that possess the activity of AD7c-NTP, are not enabled. Nevertheless, solely to expedite prosecution, Applicants have replaced the expression "40% homologous" with "90% homologous" in claim 1. Thus, the Examiner's comments, insofar as they are directed to DNA molecules that are 40% homologous to SEQ ID NO:1, are moot.

Applicants also submit that the claims, in their present form, are fully enabled by the specification. In order to satisfy the enablement requirement of 35 USC § 112, first paragraph, the claimed invention must be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *See In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). An Applicant is not limited to the confines of the specification to provide the necessary information to enable an invention. *See In re Howarth*, 654 F.2d 103, 105-6, 210 USPQ 689, 692 (CCPA 1981). An Applicant need not supply information that is well known in the art. *See Genentech, Inc. v. Novo Nordisk*, 108 F.3d 1361, 1366, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997); *Howarth*, 654 F.2d at 105-6, 210 USPQ at 692; *see also In re Brebner*, 455 F.2d 1402, 173 USPQ 169 (CCPA 1972) (finding a disclosure enabling because the procedure for making the starting material, although not disclosed, would have been known to one of ordinary skill in the art as evidenced by a

Canadian patent). Applicants assert that it would require no more than routine experimentation for a skilled artisan to practice the full scope of the presently claimed invention in view of the teachings in the specification and the knowledge available in the art. Thus, the enablement requirement of 35 USC § 112, first paragraph, is fully satisfied for claims 1-3, 5, 6, 10, 12 and 13 as currently presented.

Claims 1-3, 5, 6, 10, 12 and 13 are presently directed to, or involve the use of, a DNA construct, which comprises a DNA molecule of SEQ ID NO:1 or a DNA molecule which is at least 90% homologous thereto, wherein said DNA molecule is under control of a heterologous neuro-specific promoter, and wherein said DNA molecule codes for a protein that has an activity of AD7c-NTP when expressed in neuronal cells.

A person of ordinary skill in the art, based on the specification and the teachings generally available in the art, would be able to make and use the full scope of the claimed invention. First, a person of ordinary skill in the art would be able to generate a DNA molecule of SEQ ID NO:1 or a DNA molecule which is at least 90% homologous thereto. The specification provides methods for obtaining DNA molecules which are at least 90% homologous to SEQ ID NO:1; such methods involve the isolation of DNA molecules from cDNA libraries by hybridization under stringent conditions to the DNA molecule of SEQ ID NO:1. *See* specification at page 19, lines 3-15. Additional methods for obtaining DNA molecules for use with the claimed invention (*i.e.*, DNA molecules that are at least 90% homologous to SEQ ID NO:1), including the use of directed and random mutagenesis techniques, were well known to those of ordinary skill in the art at the time of the invention.

Once obtained, DNA molecules that are at least 90% homologous to SEQ ID NO:1 can easily be placed under the control of a neuro-specific promoter, *see, e.g.*, specification

at page 18, lines 15-27, and then tested for the ability to encode a protein having an activity of AD7c-NTP. The specification describes various methods for assaying for AD7c-NTP activity. For example, transgenic animals can be made that over-express AD7c-NTP, and, once obtained, the transgenic animals may be analyzed for evidence of neuronal or neuritic abnormalities associated with Alzheimer's disease, neuroectodermal tumors, malignant astrocytomas and glioblastomas. *See* specification at page 20, lines 1-29. Additionally, *in vitro* methods can be used which involve the overexpression of AD7c-NTP in neuronal cells and the subsequent analysis for cellular characteristics of Alzheimer's disease, including apoptosis and neuritic sprouting. *See* specification at page 46, lines 4-26. Thus, the full range of DNA molecules encompassed by, or used with, claims 1-3, 5, 6, 10, 12 and 13, can be easily made and analyzed by persons of ordinary skill in the art using only routine methods and experimentation.

The Examiner, in explaining the rejection, has emphasized the "unpredictability of the relationship between a sequence of a peptide and its tertiary structure (i.e. its activity)." *See* Paper No. 21, page 11. For instance the Examiner stated that:

> it is known for nucleic acids as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the nucleotide sequence in many instances. The effects of these changes are largely unpredictable as to which mutation has a significant effect versus not (see Chiu and Ngo).

Paper No. 21, page 13.

The relationship between the sequence of a protein and its biological function may in fact be complex, and it may be difficult to predict the exact functional consequences of a particular mutation. However, in order to practice the presently claimed invention, a

skilled artisan would not need to be able to predict the structural and/or functional consequences of particular mutations or base changes. To practice the full scope of the claimed invention, the skilled artisan would only need to be able to: (a) obtain DNA molecules that are at least 90% homologous to SEQ ID NO:1, and (b) test them for the ability to encode proteins that possess AD7c-NTP activity. As discussed above, both of these processes would be routine in the art. Admittedly, these processes may result in the production of DNA molecule that are at least 90% homologous to SEQ ID NO:1 but that *do not* encode proteins with AD7c-NTP activity. The skilled artisan, however, would be able to easily identify and discard such non-active molecules that do not fall within the scope of the claimed invention. Screening for molecules that possess a particular activity is common in the biological arts. Experimentation, even complex experimentation, is not undue if the art typically engages in such experimentation. *See In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom.*, *Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985); *see also Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.

Thus, the uncertainty that is associated with predicting protein function from sequence data is of little relevance in an analysis of the enablement of Applicants' claims. A skilled artisan would be expected to engage in screening for DNA molecules that are at least 90% homologous to SEQ ID NO:1 and that encode proteins having AD7c-NTP activity when placed under the control of a neuro-specific promoter and expressed in neuronal cells. Such screening, even if it resulted in the identification of molecule not having the desired activity, would be considered routine in the art.

The Examiner has cited Altieri *et al.*, U.S. Patent No. 6,245,523, and Frangiskakis *et al.*, *Cell 86*:59-69 (1996), as allegedly disclosing nucleotide sequences that are 74.9% and 40.8% homologous to SEQ ID NO:1, respectively. *See* Paper No. 21, page 13. The Examiner stated that the nucleotide sequence described in Altieri "inhibits cellular apoptosis," and that the nucleotide sequence described in Frangiskakis encodes a protein kinase. *See* Paper No. 21, page 13.

With respect to the nucleotide molecules disclosed in Altieri and Frangiskakis, Applicants first note that the present claims do not encompass or include nucleotide molecules that are 74.9% or 40.8% homologous to SEQ ID NO:1. Moreover, if the nucleotide molecules of Altieri and Frangiskakis encode proteins that in fact do *not* have AD7c-NTP activity (as the Examiner has asserted), then a skilled artisan would easily be able to ascertain that fact using the methods for assaying AD7c-NTP activity that are taught in the specification and that would be known to persons having ordinary skill in the art. Thus, the Examiner's discussion of the nucleotide molecules of Altieri and Frangiskakis does not provide evidence tending to cast doubt on the enablement of Applicants' claimed invention.

In view of the forgoing discussion, Applicants submit that a person having ordinary skill in the art, in view of the teachings of the specification, would be able to make and practice the full scope of Applicants' presently claimed invention. In addition, Applicants repeat their contention that the Examiner has failed to provide acceptable objective evidence or sound scientific reasoning that shows that it would require undue experimentation for a skilled artisan to make and use the claimed invention, and therefore has failed to establish a *prima facie* case of non-enablement. Accordingly, Applicants respectfully request that the

rejection of claims 1-3, 5, 6, 10, 12 and 13 under 35 USC § 112, first paragraph, be reconsidered and withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Frank R. Cottingham

Frank R. Cottingham
Attorney for Applicants
Registration No. 50,437

Date: 7/09/02

1100 New York Avenue, N.W.
Suite 600
Washington, D.C. 20005-3934
(202) 371-2600

Version with markings to show changes made

1. (Twice amended) A DNA construct, which comprises a DNA molecule of SEQ ID NO:1 or a DNA molecule which is at least [40%] 90% homologous thereto, [or a fragment thereof,] wherein said DNA molecule is under control of a heterologous neuro-specific promoter, and wherein said DNA molecule codes for a protein that has an activity of AD7c-NTP when expressed in neuronal cells.

6. (Once amended) The host cell [line] of claim 5, which is a neuronal cell.

36. (Once amended) The DNA construct of claim 1, wherein said DNA molecule codes for a protein having the amino acid sequence of SEQ ID NO:2 [or a fragment thereof].

37. (Once amended) The DNA construct of claim 1, wherein said DNA molecule consists of the DNA molecule of SEQ ID NO:1 [or a fragment thereof].

38. (Once amended) The DNA construct of claim 37, wherein said DNA molecule codes for a protein having the amino acid sequence of SEQ ID NO:2 [or a fragment thereof].

Please cancel claim 4 without prejudice or disclaimer.

Please add new claims 39-49.